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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,960	09/29/2006	Bernadette Pignol	58767.000018	6711

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EXAMINER

ZAREK, PAUL E

ART UNIT	PAPER NUMBER
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1617

MAIL DATE	DELIVERY MODE
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02/09/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/594,960	Applicant(s) PIGNOL ET AL.	
	Examiner Paul Zarek	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-32 is/are pending in the application.
- 4a) Of the above claim(s) 5, 24, 29 and 31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-23, 25-28, 30 and 32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>09/29/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Claims

1. Claims 1-32 are currently pending. This is the first Office Action on the merits of the claim(s).

Election/Restrictions

2. Applicant's election with traverse of Group I in the reply filed on 01/09/2009 is acknowledged. The traversal is on the ground(s) that the invention as claimed does not lack a special technical feature because Auvin, et al. (International Application No. WO 01/32654), do not teach an embodiment of derivative (I). Specifically, the amide linkage in the compound of Auvin, et al., is substituted *ortho* to the amine in phenothiazine ring, whereas in the instant compound, the amide linkage is in the *meta* position. This is not found persuasive because positional isomers are considered obvious variants of each other (*In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977), MPEP § 2144.09(II)). Therefore, the invention as claimed lacks inventive step, and, thus lacks a special technical feature. Acknowledgement is also made of the elected species wherein R is $-C(O)R'$ and R' is a non-substituted alkyl.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-4, 6-23, 25-28, 30, and 32 are read on the elected species and group. Claim 5 is withdrawn as being drawn to a nonelected species (R is -H). Claims 24, 29, and 31 are withdrawn as being drawn to a nonelected group.

Priority

4. Applicant's claim for the benefit of a prior-filed international application PCT/FR05/000713 (filed on 03/25/2005) under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: Applicant has not properly claimed the benefit of the prior-filed international application. To gain the benefit of a prior filed application, "[t]he later-filed application must contain a reference to the prior-filed application in the first sentence(s) of the specification or in an application data sheet, for a benefit claim under 35 U.S.C. 120, 121, or 365(c), and also for a benefit claim under 35 U.S.C. 119(e)." (MPEP 201.11(C)). The effective filing date of the instant application is 09/29/2006.
5. Acknowledgment is made of applicant's claim for foreign priority to French applications 0403203 and 0406404 (filed on 03/29/2004 and 06/14/2004) under 35 U.S.C. 119(a)-(d). The French applications were filed more than a year prior to the filing of the instant application, and, hence, Applicant cannot claim priority to said documents. There is currently no foreign priority of the instant application. Applicant may gain the foreign priority by perfecting the claim for the benefit of the prior-filed international application PCT/FR05/000713.

Claim Rejections - 35 USC § 112 (1st paragraph)

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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7. Claims 1-4, 6-19, 21-23, 25-28, and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating hearing loss comprising administration of a composition comprising derivative (I) within 24 hours of loss of hearing, or inhibiting, ameliorating, or reducing the severity of hearing loss comprising administration of derivative (I) up to two days prior to hearing loss, does not reasonably provide enablement for preventing hearing loss, treating pathologies associated with hearing loss, or treating hearing loss by administration of derivative (I) more than 24 hours after the loss of hearing, or inhibiting, ameliorating, or reducing the severity of hearing loss comprising administration of derivative (I) more than two days prior to the loss of hearing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

8. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” (MPEP § 2164.01(a))

a. *The breadth of the claim*: Claims 1-4, 6-11, 13-19, 21-23, 25-28, and 32 are drawn to a method of treating hearing loss comprising administration of derivative (I) at any time following the hearing loss. Claims 1-4, 6-12, 14-19, 21-23, and 25-28 are drawn to a method of preventing hearing loss comprising administration of derivative (I) at any time prior to the hearing loss.

“Prevent,” “prevention,” and “prophylaxis” are potent terms implying that the method of prevention, or a prophylactic agent will necessarily prevent all hearing loss in

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every subject that receives derivative (I). If even one subject who receives derivative (I) as in a preventative fashion, has its hearing reduced by any amount, then the method is not considered prevention;

b. *Nature of the invention*: The nature of the invention is a method of treating, inhibiting, ameliorating, or reducing the severity of hearing loss comprising the administration of derivative (I) between the time points of 2 days prior to the hearing loss to 24 hours following the hearing loss;

c. *The state of the prior art*: Takumida, et al. (Acta Otolaryngologica, 2003, provided in IDS), teach that nitric oxide (NO) and reactive oxygen species (ROS) both contribute to inner ear damage, and that ROS scavengers and calpain inhibitors have been effectively utilized to treat inner ear damage (pgs 11-12, "Discussion). Franze, et al. (International Journal of Audiology, 2003, provided in IDS) teach that allopurinol, a known ROS scavenger, can protect guinea pigs from hearing loss. In this model, the animals were administered allopurinol multiple times in the 24 hours prior to acoustic trauma. Thirty days after the trauma, the guinea pigs recovered most, but not all, of their hearing (Figs 3-6). Franze, et al., further teach that their data suggest that the protective effect occurs only during the first 2 hours of noise exposure (pg 233, paragraph 5). Wang, et al. (NeuroReport, 1999, provided in IDS) teach that the calpain inhibitor, leupeptin, reduced noise-induced cochlear damage and hearing loss (abstract);

d. *Level of one of ordinary skill in the art*: Medicinal chemists, scientists and physicians investigating the molecular basis of hearing loss would comprise one of ordinary skill in the art;

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- e. *Level of predictability in the art:* The art is in agreement that hearing loss is mediated by ROS and calpain, and that reducing the concentration of ROS or inhibiting calpain protects an organism from hearing loss;
- f. *Amount of direction provided by the inventor:* Applicants provide a phenothiazine compound (derivative (I)) that combines antioxidizing agent (phenothiazine) and a calpain inhibitor (the leucine-furanyl moiety). Applicants state that these compounds were described in Auvin, et al. (International Application WO 01/32654, provided in IDS) (pg 6, lines 1-2). Auvin, et al., disclose that the compounds disclosed therein can inhibit calpain and trap ROS (abstract);
- g. *Existence of working examples:* Applicants demonstrate that administration of derivative (I) to guinea pigs in a prophylactic model of acoustic trauma results in a near full recover of hearing (Fig 3). It is noted, however, that the subjects did not fully recover their hearing, as the line measuring hearing loss in Fig 3 dips below 0 (which represents no change in hearing sensitivity) at higher frequencies. Fig. 9 demonstrates that administration of derivative (I) following acoustic trauma within 7 hours results in about 50% recovery of hearing. Administration of derivative (I) 24 hours post-trauma still maintains a treatment effect, although it is not robust (e.g. about 5-10% recover); and,
- h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure:* The prior art acknowledges both in theory and practice that ROS scavengers and calpain inhibitors are effect agents to treat hearing loss when given near the time of loss of hearing. Both suggest this therapeutic effect diminishes as the

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time between administration and the hearing loss increases. Where Franze, et al., suggest that the ROS scavenger (e.g. allopurinol) must be administered within 2 hours of hearing loss, the instant specification demonstrates efficacy as late as 24 hours post trauma. The prior art and the instant specification also demonstrate that when administered acutely prior to hearing loss, the agents can reduce the severity of the hearing loss, but does not completely inhibit hearing loss. Undue experimentation would be required to use the invention as claimed.

Claim Rejections - 35 USC § 112 (2nd paragraph)

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 14 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is drawn to a method wherein derivative (I) is administered following the administration of a medicament. Claim 21 is drawn to a method wherein derivative (I) is administered in combination with another substance of "pharmaceutical activity." Such limitations are incomprehensibly broad as to render unclear the metes and bounds of these limitations.

11. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 recites the limitation "any pathologies associated with hearing loss" in lines 4-5. There is insufficient antecedent basis for this limitation in the claim. "Pathologies

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associated with hearing loss” is broader than “hearing loss” which is recited in Claim 1, from which Claim 22 depends.

12. Claims 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 12 and 13 recite the limitation that derivative (I) be administered in a “pre-treatment” or a “post-treatment,” respectively. It is unclear what the reference treatment is. For art purposes, Examiner is interpreting "pre-treatment" and "post-treatment" to be methods of prevention and treatment, respectively.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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15. Claims 1-4, 6-23, 25-28, 30, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seidman (Laryngoscope, 2000, provided in IDS) in view of Takumida, et al. (above), and Auvin, et al. (above).

16. Claim 1 of the instant application is drawn to a method of preventing and treating hearing loss in a subject comprising administration of derivative (I). Claims 2-4 and 6-11 limit the structure and stereochemistry of derivative (I). Claims 12 and 13 are drawn specifically to methods of prevention (derivative (I) administered prior to hearing loss) and treatment (derivative (I) administered after hearing loss), respectively. Claims 14-17 limit the method such that derivative (I) is administered following the administration of a generic medicament (Claim 14) or a specific medicament (Claims 15-17). Claims 18-20 limit the method to treat or prevent hearing loss due to prebycusis (Claim 18) or acoustic traumatism (Claims 19-20). Claim 20 limits the time period in which derivative (I) is administered (within 7 hours). Claims 21-23 limit derivative (I) to be combined with a generic substance with pharmaceutical activity (Claims 21 and 22) or specific substance (Claim 23). Claims 25-28, 30, and 32 are not further limiting over Claims 14 and 16-20. Art that reads on Claims 14 and 16-20 will necessarily apply to Claims 25-28, 30, and 32.

17. Seidman teaches that there is a “direct correlation” between hypoxia and decreased hearing sensitivity (pg 729, col 1, paragraph 3, lines 2-3). Hypoxia induces the production of ROS (ROM in Seidman), which is associated with cochlear ischemia, noise (e.g. acoustic) trauma, aging, and presbycusis (pg 736, col 1, paragraph 3, lines 1-3). Seidman also teaches that dietary restriction or nutrient supplementation which reduce ROS “provide an internal milieu that is favorable to the organism,” that is, treats or reduces the severity of hearing loss (pg 736, col 2,

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paragraph 2, lines 5-8). Seidman further teaches that different antioxidants affect hearing loss to differing degrees, and suggests combining antioxidants to maximize their effect (pg 736, col 2, paragraph 2, lines 16-20). Takumida, et al., teach that NO and ROS play a central role in inner ear damage (pg 8, col 1, paragraph 1, lines 1-10). ROS scavengers, NMDA receptor antagonists, calcium channel blockers (which induce vasodilation), and calpain inhibitors have been reported to protect the inner ear from damage, *in vivo* (pg 11, col 2, paragraph 2, line 1 to pg 12, col 1, paragraph 1, line 6). Takumida, et al., also teach that some drugs, such as cisplatin and gentamicin can cause inner ear damage both by inducing ROS production (pg 12, col 1, paragraph 1, lines 17-20).

18. Collectively, Seidman and Takumida, et al., teach that inner ear damage, which can cause hearing loss, is directly associated with increases in ROS, and that ROS scavengers are effective for treatments for hearing loss, provided they are administered proximal to the loss of hearing. NMDA receptor antagonists, vasodilators, antioxidants and calpain inhibitors are known to treat hearing loss, as well. Moreover, ROS scavengers can reduce the severity of loss of hearing as well. The prior art teaches that common pharmaceutical therapies (i.e. cisplatin and gentamicin), excessive noise (e.g. acoustic trauma), and aging (e.g. presbycusis) can lead to hearing loss. All of these are amenable to treatment by a ROS scavenger.

19. By combining Seidman and Takumida, et al., a skilled artisan would understand to use compounds that are known to scavenge ROS for the treatment of hearing loss. It would have been *prima facie* obvious to said artisan to combine an ROS scavenger with an NMDA receptor antagonist, vasodilators, antioxidant, and/or calpain inhibitor, since they are all known to achieve the same result (e.g. amelioration of hearing loss). The skilled artisan would be

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motivated to provide an ROS scavenger concurrently with antibiotics, such as gentamicin, or anticancer drugs, such as cisplatin, which are known to induce hearing loss and that this hearing loss is amenable to treatment by ROS scavengers.

20. Seidman and Takumida, et al., do not teach a method of treating hearing loss with derivative (I).

21. The instant application discloses that the compounds of derivative (I) are described in Auvin, et al. They consist of a phenothiazine, which is a known oxygen scavenger, and a moiety that inhibits calpain. Auzin, et al., discloses that the compounds taught therein possess “calpain inhibiting activity and/or an activity trapping reactive oxygen species” (abstract). Moreover, Auzin, et al., teaches the elected species, (3S)-3-((2S)-r-methyl-2-[(10H-phenothiazin-2-ylcarbonyl)amino]pentanoyl} amino)tetrahydro-2-furanyl acetate (pg 27, lines 13-14).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to use the species taught by Auzin, et al., which is disclosed to possess both ROS trapping and calpain inhibiting capabilities, to treat hearing loss, which is known to be amenable to treatment by ROS scavengers and calpain inhibitors.

Conclusion

22. Claims 1-4, 6-19, 21-23, 25-28, and 32 are rejected.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Rita J. Desai/
Primary Examiner, Art Unit 1625